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An enantioselective catalytic approach to *syn* deoxypropionate units combining asymmetric Cu-catalyzed 1,6- and 1,4-conjugate addition

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Dedicated to Professor Henri B. Kagan on the occasion of his 80th birthday

ABSTRACT

A novel iterative approach to the synthesis of the naturally ubiquitous *syn* deoxypropionate motif is reported. The route comprises a new Horner–Wadsworth–Emmons reagent to prepare α,β,γ,δ-bisunsaturated thioesters. Next, two Me-substituents are introduced in high yield, regio- and enantioselectivity using sequential asymmetric Cu-catalyzed 1,6-conjugate addition, base-catalyzed olefin isomerization and Cu-catalyzed enantioselective 1,4-conjugate addition. After reduction to the aldehyde these transformations can be repeated to install three or more Me groups with a *syn* 1,3-relationship.

1. Introduction

The enantioselective synthesis of the biologically relevant polydeoxypropionate motif has been a topic of intensive research in recent years.[1] As a consequence, a number of highly efficient catalytic iterative methods have been developed.[1] In particular, the methods based on asymmetric zirconium-catalyzed carboalumination,[2] as well as iterative Ir-catalyzed hydrogenation[3] and asymmetric Cu-catalyzed conjugate addition (1,4-ACA)[4,5] have been employed successfully to synthesize a variety of biologically relevant lipids.[6]

Although the described methods feature high enantioselectivity in combination with low catalyst loading and high yield, alternative routes are still highly warranted. Recently, we reported the asymmetric catalytic 1,6-addition[7] (1,6-ACA) providing access to δ-substituted β,γ-unsaturated esters and thioesters **2** (Scheme 1). We envisioned that subsequent isomerization to the α,β-unsaturated thioester **3** followed by 1,4-ACA[4] would provide an efficient route to construct 1,3-dimethyl arrays **4**. Herein we report the combined use of 1,6-ACA[7] and 1,4-ACA[4] in a new protocol for the construction of deoxypropionate subunits.

2. Results and discussion

A first prerequisite for a straightforward route to deoxypropionate units is facile access to α,β,γ,δ-bisunsaturated thioesters (Scheme 2). Current methods for the synthesis of α,β,γ,δ-bisunsaturated thioesters comprise thioesterification of an α,β,γ,δ-bisunsaturated acid (route a),[8] as well as Wittig olefination of α,β-unsaturated aldehydes (route b).[9,10] However, for our envisioned iterative route we developed the novel extended Horner–Wadsworth–Emmons (HWE) reagent **11**. Coupling of **11** with an aldehyde **10** would provide a general route to a variety of α,β,γ,δ-bisunsaturated thioesters (route c).

Using isobutyraldehyde **10c** and the conditions reported for the extended HWE reaction[11] with the oxoester analogue of **11**,[12] the product **7c** was obtained in low, poorly reproducible yields but excellent *E*/*Z*-selectivity (Table 1, entry 1). The use of LHMDS as a base improved the yield slightly but still gave poorly reproducible results (entry 2). Optimization of the reaction conditions identified that strict temperature control (addition of aldehyde at −78 °C and allowing the reaction to warm up in 30 min to −40 °C) in combination with high dilution conditions (0.039 M in **10c**) for the reaction was essential to give **7c** in good and reproducible yield and excellent *E*/*Z*-selectivity (entry 3).[†] With these optimized conditions the aldehydes **10d** and **10e** were converted and the desired α,β,γ,δ-bisunsaturated thioesters **7d** and **7e** were obtained in lower, but acceptable, yields (entries 4 and 5). Presumably, the more accessible α-H of **10d** and **10e** compared to the sterically encumbered α-H in **10c** causes side reactions to occur. Finally, DIBAL-H reduction and extended HWE reaction of **12**[‡] provided the chiral 1,6-ACA substrate **7f** in 64% yield over two steps (Scheme 3).

With the substrates in hand, the scope of the 1,6-ACA[7] of MeMgBr[§] was explored (Table 2). Employing CuBr·SMe_2 and (+)-reversed Josiphos **L1**, the 1,6-ACA of MeMgBr to substrate **7b** proceeds

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[†] All reported yields are for reactions at a 0.5 mmol scale. The reaction was performed at a larger scale with the conditions reported for entry 2 and gave low yield (~30%). Presumably strict control of the temperature is needed to obtain good yields at a larger scale.

[‡] For the synthesis of **12** see the Experimental.

[§] A limitation of the current method was discovered when **7a** was subjected to 1,6-ACA of the more reactive EtMgBr or *n*BuMgBr leading to the 1,6-addition products in high yield and regioselectivity but moderate enantioselectivity.

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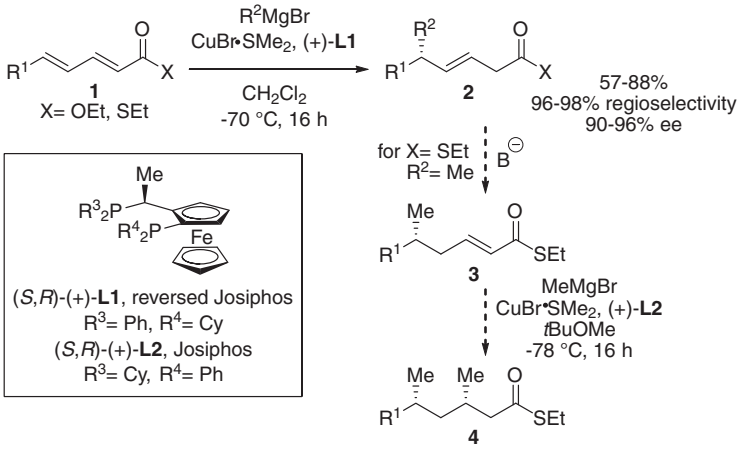
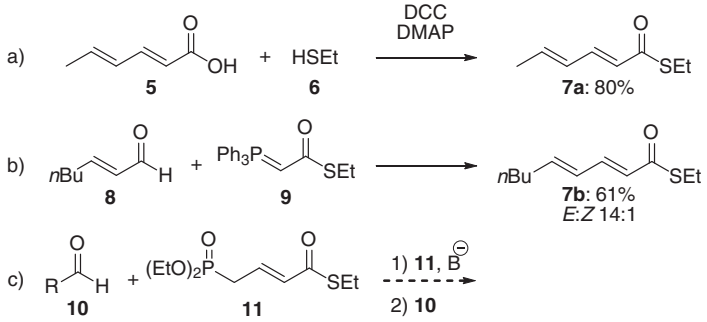
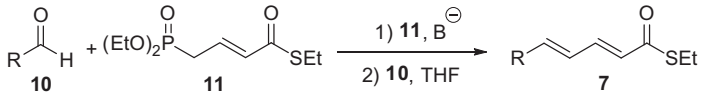


Scheme 1. Asymmetric catalytic 1,6-addition and envisioned route to deoxypropionate units.



Scheme 2. Synthetic routes to α,β,γ,δ-bisunsaturated thioesters. Reagents and conditions: route a: **5**, **6** (1.3 equiv), DCC (1.05 equiv), DMAP (0.1 equiv) in CH_2Cl_2 (0.22 M in **5**), 0 °C to RT, 16 h; route b: **8**, **9** (1.3 equiv) in CH_2Cl_2 (0.14 M in **8**), 40 °C, 20 h.

Table 1
HWE reaction leading to α,β,γ,δ-bisunsaturated thioesters[a]



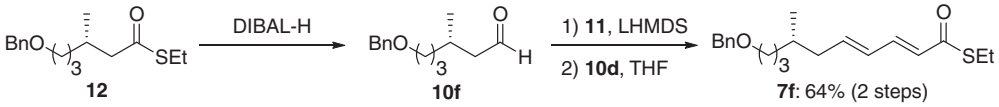
Entry	Aldehyde	Product	Base	Conditions step 2	Molarity (M)	Yield[b] (%)
1	**10c**; R = *i*Bu	**7c**	LDA	−78 °C to RT, 3 h	0.074	50[c]
2	**10c**; R = *i*Bu	**7c**	LHMDS	−78 to −40 °C, 16 h	0.29	70[d]
3	**10c**; R = *i*Bu	**7c**	LHMDS	−78 to −40 °C, 16 h	0.039	70
4	**10d**; R = CH_2Bn	**7d**	LHMDS	−78 to −40 °C, 16 h	0.039	39
5	**10e**; R = $(CH_2)_3OBn$	**7e**	LHMDS	−78 to −40 °C, 16 h	0.039	47

[a] Conditions: entry 1: (1) **11** (1.43 equiv), LDA (1.4 equiv), THF (0.13 M in **11**), −78 to −20 °C, 3 h, then (2) **10c**, THF (total 0.074 M in **10c**); entry 2: **11** (1.5 equiv), LHMDS (1.4 equiv), THF (0.63 M in **11**), −78 °C, 0.5 h, then (2) **10c**, THF (total 0.29 M in **10c**); entries 3–5: **11** (1.5 equiv), LHMDS (1.4 equiv), THF (0.07 M in **11**), −78 °C, 0.5 h, then 2) **10**, THF (total 0.039 M in **10**).
[b] In all cases the products were obtained with over 95:5 *E*/*Z*-ratio according to ^1H NMR.
[c] Yields in the range of 30–50% were obtained.
[d] Yields in the range of 30–70% were obtained.

in high yield and excellent regio- and stereoselectivity (entry 1). When the more bulky ζ-Me-substituted substrate **7c** was subjected to 1,6-ACA, a slight drop in regio- and enantiocontrol was observed (entry 2). This drop in regio- and enantioselectivity is a continuing trend; the more sterically encumbered the R-groups the lower both enantio- and regioselectivity for the 1,6-ACA are.[¶] The substrates incorporating a phenyl- or benzyl-protected hydroxy functionality gave good yields and good to excellent regio- and stereocontrol (entries 3 and 4). Finally, the ability of the catalyst to override substrate control[13] was tested by the 1,6-ACA of MeMgBr to chiral substrate **7f**. *Syn*-addition proceeded in high yield, regio- and diastereoselectivity (entry 5), while *anti*-addition gave high yield and regioselectivity, but moderate diastereoselectivity (entry 6).

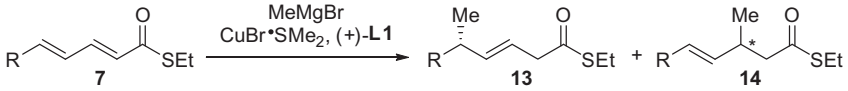
For the next step in the iterative sequence, the isomerization to the α,β-unsaturated thioester **15b**, a variety of methods were investigated. The olefin was resistant to isomerization by heat (xylene, 140 °C) and various transition metal catalysts ($Pd(OAc)_2$, $Pd(PPh_3)_4$, Wilkinsons catalyst, and $RuCl_3$). Base-catalyzed

[¶] This trend is even more apparent when the results in Table 2 are compared to the results of 1,6-ACA to the R=Et substituted α,β,γ,δ-bisunsaturated thioester reported in Ref. 7 (93% ee and 97% regioselectivity).



Scheme 3. Synthesis of the chiral 1,6-ACA substrate **7f**. Reagents and conditions: reduction: **12**, DIBAL-H (1.2 equiv), CH_2Cl_2 (0.29 M in **12**), −75 °C, 3 h; extended HWE reaction: see Table 1, entries 3–5.

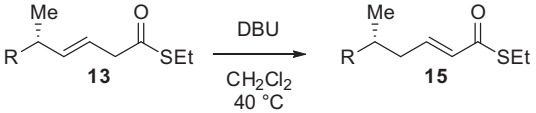
Table 2
1,6-ACA to α,β,γ,δ-bisunsaturated thioesters[a]



Entry	Substrate	Product	Yield[b] (%)	**13**:**14**[c]	ee[d] (%)
1	**7b**, R = *n*Bu	**13b**	83	99:1[e]	89
2	**7c**, R = *i*Bu	**13c**	84	95:5	82
3	**7d**, R = CH_2Bn	**13d**	78	99:1[e]	82
4	**7e**, R = $(CH_2)_3OBn$	**13e**	86	94:6	86
5[f]	**7f**, R = $CH_2((R)$-CHMe$)(CH_2)_3OBn$	**13f**	88	85:15	(87:13)[g]
6[h]	**7f,** R = $CH_2((R)$-CHMe$)(CH_2)_3OBn$	**13g**	83	87:13	(22:78)[g]

[a] Conditions: **7** in CH_2Cl_2 was added to a solution of MeMgBr (3.0 M in Et_2O, 2.0 equiv), (+)-**L1** (5.25 mol %) and CuBr·SMe_2 (5 mol %) in CH_2Cl_2 (0.2 M in **7**), −70 °C, 16 h.
[b] Yields include both **13** and **14**.
[c] Ratio of **13**:**14** was determined by ^{1}H NMR.
[d] Enantioselectivity was determined by chiral GC or HPLC.
[e] Ratio of **13**:**14** was determined by chiral GC or HPLC.
[f] Compound **7f** was prepared in 93% ee.
[g] Diastereoselectivity *syn*:*anti*.
[h] Compound **7f** was prepared in 93% ee, (−)-**L1** was used.

Table 3
Isomerization of β,γ-unsaturated thioester **13** to α,β-unsaturated thioester **15**[a]



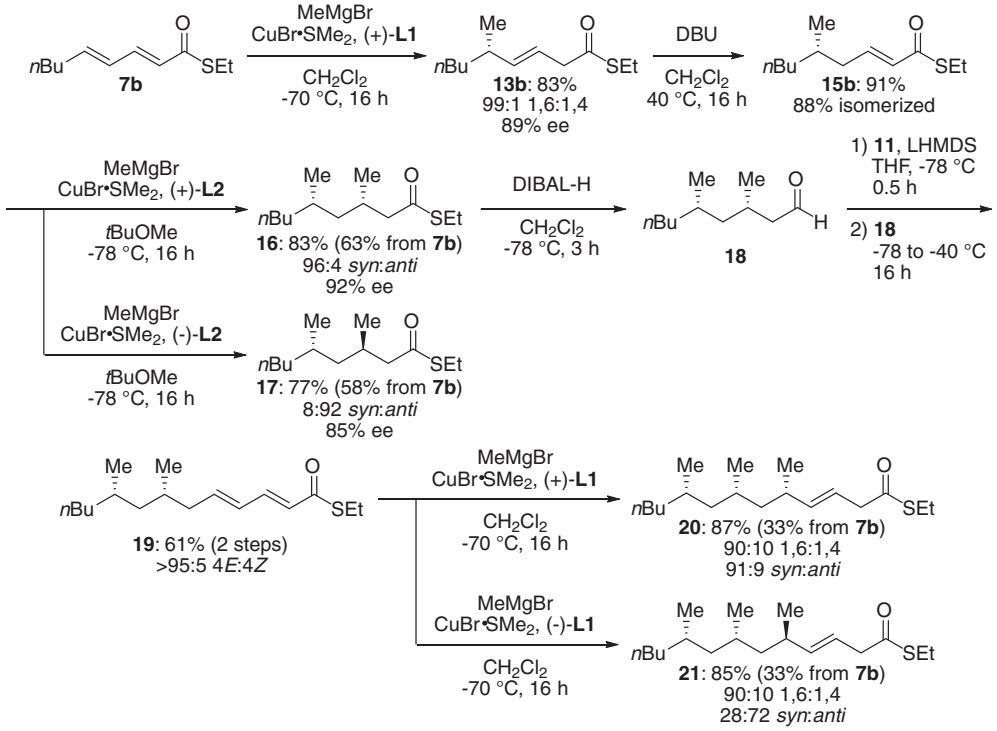
Entry	Substrate	Product	Equiv DBU	Reaction time (h)	**13**:**15**[b]	Yield[c] (%)
1	**13b**; R = *n*Bu	**15b**	0.1	16	50:50	88
2	**13b**; R = *n*Bu	**15b**	1.5	16	20:80	87
3	**13b**; R = *n*Bu	**15b**	5	16	12:88	88
4	**13b**; R = *n*Bu	**15b**	10	16	12:88	88
5	**13b**; R = *n*Bu	**15b**	10	64	15:85	90
6	**15d**; R = CH_2Bn[d]	**15d**	5	16	11:89	n. d.

[a] Conditions: **13** or **15** and DBU in CH_2Cl_2 (0.1 M in **13** or **15**), 40 °C.
[b] Ratio of **13**:**15** was determined by GC–MS.
[c] Yields reported are combined yields for **13**, **15** and the traces of **14** present from the 1,6-ACA.
[d] Pure isolated **15d** was used.

isomerization employing DBU was more effective to isomerize the double bond into the desired position (Table 3, entries 1 and 2). Optimization of the amount of DBU used for this transformation identified that 5 equiv of DBU was optimal for isomerization in 16 h (entry 3).[‖] Employing the conditions described in entry 3, the α,β-unsaturated product **15** was obtained without racemization of the asymmetric Me-center.[††] Use of more DBU did not lead to full isomerization (entries 4 and 5). Furthermore, exposing isolated α,β-unsaturated thioester **15d** once more to the reaction conditions gave a mixture of β,γ-unsaturated thioester **13d** and α,β-unsaturated thioester **15d** (entry 6) indicating an equilibrium.

To test our alternative synthetic strategy for the iterative construction of deoxypropionate units, several Me-centers starting from **7b** were introduced (Scheme 4). Both the *syn*-**16** and *anti*-product **17**, incorporating two Me-substituents, were obtained in good overall yield (respectively, 63% and 58% over three steps), regio-, and stereoselectivity.[‡‡,§§] Subsequent chain elongation gave the 1,6-ACA substrate **19** in good yield and excellent *E*/*Z* ratio. Finally, synthesis of the *syn*,*syn*-1,6-ACA product **20** proceeded in good yield, regio-, and diastereoselectivity while the *syn*,*anti*-1,6-ACA product **21** was obtained in good yield and regioselectivity but mediocre diastereoselectivity.

[‖] Due to the hydrophobic nature of the obtained products attempts to separate the two regioisomers were unsuccessful. Fortunately, the presence of these impurities did not affect the subsequent 1,4-ACA.
[††] For the conversion of **13d** to **15d** no racemization was observed using chiral HPLC (see Experimental).
[‡‡] The lower enantio- and diastereoselectivity of the 1,4-ACA on **15b** compared to the results reported in ref 4d can be explained by the lower ee of **15b** (89% ee vs 95% ee).
[§§] Although separation of **13b**, the 1,4-addition side-product of the 1,6-ACA (**14b**) and **15b** in earlier stages of the synthesis was not possible, at this stage the pure mixture of the saturated products **16** and **17** was obtained successfully.

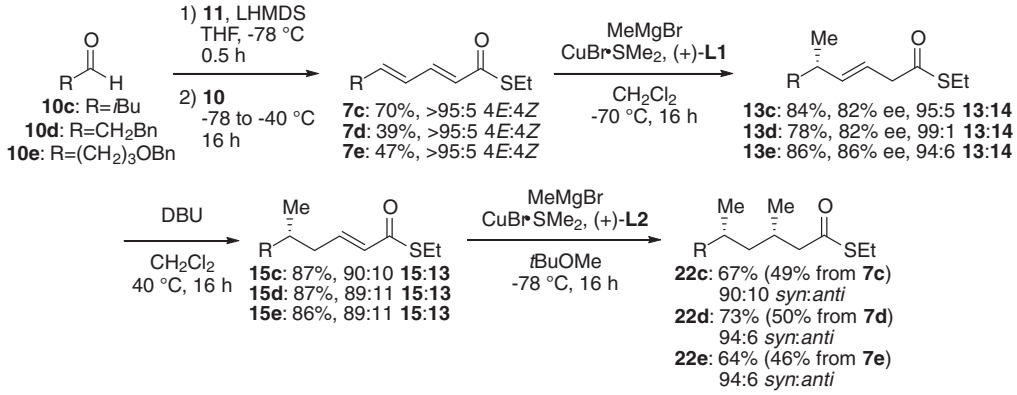


Scheme 4. Iterative construction of deoxypropionate units starting from **7b**. Reagents and conditions: 1,6-ACA: see Table 2; isomerization: see Table 3; 1,4-ACA: **15b** in *t*BuOMe was added to a solution of MeMgBr (3.0 M in Et_2O, 1.5 equiv) and **L1**–CuBr·SMe_2 complex (1.0 mol %) in *t*BuOMe (0.2 M in **7**), −78 °C, 16 h; Reduction and chain elongation: see Scheme 3; 1,6-ACA: see Table 2. Yield for the 1,6-ACA includes **13** and **14**; Yield for the isomerization step includes **13**, **15** and **14**; Yield for the subsequent 1,4-ACA includes only **16** and **17**.

The generality of the construction of deoxypropionate units via consecutive 1,6-ACA-isomerization-1,4-ACA was illustrated by the introduction of two consecutive Me groups on several functionalized substrates (Scheme 5). In all cases the products comprising two deoxypropionate units were obtained in good yield, regio-, and diastereoselectivity.

3. Conclusion

In conclusion, we have developed an alternative method for the construction of deoxypropionate units exploiting Cu-catalyzed 1,6-ACA[7] and 1,4-ACA.[4d] To allow iterative construction of deoxypropionate units a novel method for the construction of α,β,γ,δ-bis-unsaturated thioesters and an alternative method for the construction of α,β-unsaturated thioesters were developed. The novel route was used for the construction of several Me-centers in a *syn*-1,3-fashion and the corresponding products were obtained in good yield, regio-, and enantioselectivity. It must be noted that the current methodology is suited for the construction of *syn*-deoxypropionate units; while the *anti*-deoxypropionate units are presumably constructed more efficiently by the 1,4-ACA.[4d] A drawback of the current method is the slightly lower enantioselectivity obtained for the 1,6-ACA of MeMgBr to α,β-unsaturated thioesters compared to the corresponding enantioselectivities for the 1,4-ACA.[4d] However, this drawback is readily circumvented by the construction of the first stereogenic center by 1,4-ACA,[4d] subsequent chain elongation, and 1,6-ACA taking advantage of the inherent preference[13] for the formation of *syn* deoxypropionate units. Compared to the optimized iterative route for the construction of deoxypropionate



Scheme 5. Iterative construction of deoxypropionate units on several functionalized substrates. Reagents and conditions: extended HWE: see Table 1; 1,6-ACA: see Table 2; isomerization: see Table 3; 1,4-ACA: see Scheme 4. Yield for the 1,6-ACA include **13** and **14**; yield for the isomerization step include **13**, **15** and **14**; Yield for the subsequent 1,4-ACA include only *syn*-**22** and *anti*-**22**.

units via 1,4-ACA employing either Josiphos[4d] **L2** or Tol-BINAP[4c] our newly developed methodology seems competitive.

4. Experimental

4.1. General procedures

Thin-layer chromatography (TLC) was performed on commercial Kieselgel 60F_{254} silica gel plates and compounds were visualized with $KMnO_4$ reagent. Flash chromatography was performed on silica gel. Drying of solutions was performed with $MgSO_4$. Concentration of solutions was conducted with a rotary evaporator. Progress of the reactions and conversion was determined by GC–MS (GC, HP6890; MS, HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA). Enantio- and regioselectivities were determined by capillary GC analysis (HP6890, Chiraldex-B-PM 30 m × 0.25 mm × 0.25 μm; HP6890, Chiralsil-DEX-CB 25 m × 0.25 mm × 0.25 μm) using flame ionization detection or HPLC (chiralcel OB-H, 4.6 × 250 mm, 5 m, 40 °C, 0.5 mL/min, 210 nm; chiralcel OJ-H, 4.6 × 250 mm, 5 m, 40 °C, 0.5 mL/min, 210 nm) (in comparison with authentic samples of racemates of 1,6- and 1,4-addition products). Optical rotations were measured in CH_2Cl_2 or $CHCl_3$ on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). ^{1}H NMR spectra were recorded at 400 MHz with $CDCl_3$ as a solvent (Varian AMX400 spectrometer). ^{13}C NMR spectra were obtained at 100.59 MHz in $CDCl_3$. The nature of the carbon was determined from APT ^{13}C NMR experiments. Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, δ = 7.26 for hydrogen atoms, δ = 77.16 for carbon atoms). The following abbreviations were used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. High resolution mass spectra were determined on a AEI-MS-902 mass spectrometer by EI (70 eV) measurements or on a FTMS Orbitrap FischerScientific mass spectrometer by ESI measurements in positive mode. Fragmentation patterns were determined by GC–MS (GC, HP6890; MS, HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA). All reactions under N_2 atmosphere were conducted using standard Schlenk techniques. CH_2Cl_2 was distilled from CaH_2 under N_2 prior to use. THF was distilled from Na using benzophenone as an indicator under N_2 prior to use. *t*BuOMe was distilled from CaH_2 under N_2 prior to use. CuBr·SMe_2 was purchased from Sigma–Aldrich. (+)-(*S*,*R*)-Reversed Josiphos, (−)-(*R*,*S*)-reversed Josiphos, (+)-(*S*,*R*)-Josiphos and (−)-(*R*,*S*)-Josiphos were purchased from Sigma–Aldrich. For Josiphos the prepared CuBr complexes were used.[4c] MeMgBr was purchased from Sigma–Aldrich and was titrated using sBuOH and catalytic amounts of 1,10-phenanthroline before use.

Diethyl phosphonoacetaldehyde diethyl acetal, crotonic acid, *N*-bromosuccinimide, EtSH, DCC, triethyl phosphite, sorbic acid, isovaleraldehyde, DBU, and DIBAL-H were purchased from Sigma–Aldrich. Azobis(isobutyronitrile) was purchased from Janssen Chimica. DMAP, (*E*)-2-heptenal, and hydrocinnamylaldehyde were purchased from ACROS. EDC-HCl salt was purchased from Fluka.

S-Ethyl 2-(triphenylphosphoranylidene)ethanethioate was prepared as described in Ref. 9. Triethylphosphonocrotonate was purchased from Aldrich (90% technical grade) and purified by column chromatography (gradient Et_2O/pentane 25:75 to Et_2O) to give pure (2*E*)-triethylphosphonocrotonate.

All spectral data are available via the authors and at the www via the library of the University of Groningen via this link: http://ir.ub.rug.nl/search.php?Query=An+enantioselective+catalytic+approach+to+syn+deoxypropionate+units+combining+asymmetric+Cu-catalyzed+1%2C6-+and+1%2C4-conjugate+addition&Archive=&SearchIn=&Year=.

Data in Section 4 is ordered as follows:

1. Synthesis of HWE-reagent **11** (Scheme 6).
2. Synthesis of 1,6-ACA substrates.
3. Synthesis of 1,6-ACA products.
4. Synthesis of 1,4-ACA substrates.
5. Synthesis of 1,4-ACA products.

4.1.1. Route 1 (Scheme 6)[¶¶]

4.1.1.1. Unmasking of aldehyde from acetal S1. In a round-bottomed flask equipped with stirring bar, the acetal **S1** (1.1 mL, 4.6 mmol) was dissolved in an aq 1% HCl solution (30 mL). After 8 h stirring at room temperature the reaction mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with an aq $NaHCO_3$ solution (saturated, 2 × 30 mL), dried, and concentrated to a colorless oil and immediately used for the Wittig reaction. [~30% yield (unoptimized), colorless oil].

Diethyl 2-oxoethylphosphonate **S2** data in accordance with data described in Ref. 14.

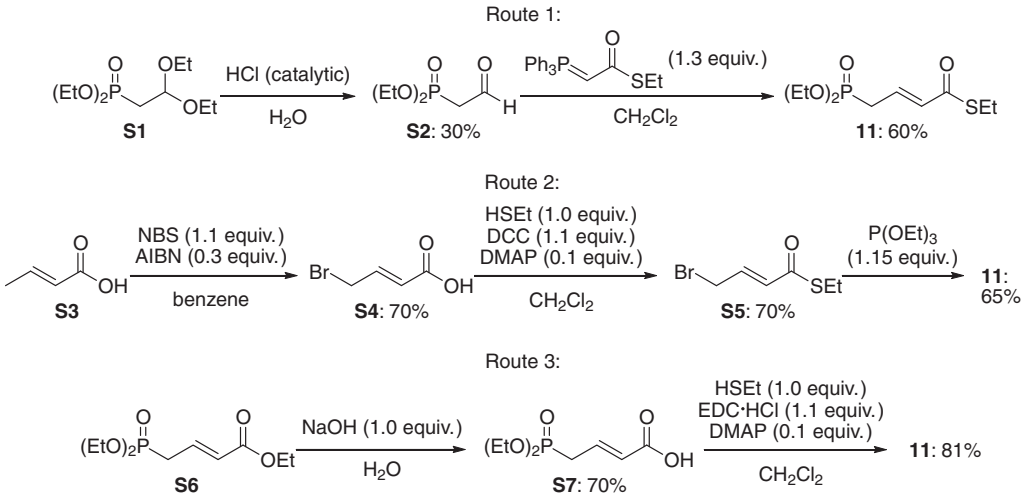
4.1.1.2. Wittig reaction of S2. In a round-bottomed flask equipped with stirring bar under a N_2 atmosphere, *S*-ethyl 2-(triphenylphosphoranylidene)ethanethioate (1.49 g, 4.09 mmol, 1.3 equiv) was dissolved in anhydrous CH_2Cl_2 (30 mL). The aldehyde **S2** (0.57 g, 3.15 mmol, 1.0 equiv) was added, the reaction mixture was heated to reflux and stirred for 48 h, allowed to cool to room temperature, and stirred for 4 days at room temperature. The reaction mixture was then concentrated and the remaining solid was extracted with *n*-pentane (3 × 10 mL). The combined organic extracts were concentrated to a yellow oil. Flash column chromatography (gradient EtOAc/pentane 50:50 to EtOAc) yielded **11** as a colorless oil (yield ~60%) with a minor impurity of triphenylphosphine oxide. (*E*)-*S*-Ethyl 4-(diethoxyphosphoryl)but-2-enethioate **11**: [~60% yield, colorless oil mixed with some white solid]. For spectroscopic data vide infra.

4.1.2. Route 2 (Scheme 6)

4.1.2.1. Bromination of crotonic acid[15]. In a round-bottomed flask equipped with stirring bar, crotonic acid (20 g, 0.23 mol, 1.0 equiv) and *N*-bromosuccinimide (46 g, 0.25 mol, 1.1 equiv) were dissolved in benzene (200 mL). After the solution was heated at reflux, azobis(isobutyronitile) (1.14 g, 6.97 mmol, 3 mol %) was added and refluxing was continued for 2 h. Then the reaction solution was cooled to 0 °C and filtered over Celite. The residue was washed with toluene (50 mL). The filtrate was concentrated and recrystallized from toluene to yield **S4** as a white solid in several batches. (*E*)-4-bromobut-2-enoic acid (4-bromocrotonic acid) **S4**: [70% yield, white solid, melting point: 74.7–75.3 °C]. ^{1}H NMR δ 11.63 (s, br, 1H), 7.10 (dt, J = 7.3 Hz, 15.3 Hz, 1H), 6.03 (d, J = 15.4 Hz, 1H), 4.01 (d, J = 7.3 Hz, 2H), spectrum contains traces of crotonic acid; ^{13}C NMR δ 171.3 (C), 144.65 (CH), 123.99 (CH), 28.86 (CH_2); MS m/z 166 ($M^+[Br^{81}]$, 56), 164 ($M^+[Br^{79}]$, 56), 85 (M−Br, 100); HRMS calcd for $C_4H_5BrO_2$ 163.9473, found 163.9471.

4.1.2.2. Thioesterification of 4-bromocrotonic acid[16]. In a round-bottomed flask equipped with stirring bar under a N_2 atmosphere, 4-bromocrotonic acid **S4** (3.47 g, 21.02 mmol, 1.0 equiv), EtSH (1.55 mL, 21.02 mmol, 1.0 equiv), and DMAP (0.26 g, 2.10 mmol, 0.1 equiv) were dissolved in CH_2Cl_2 (120 mL), the solution was cooled to 0 °C and DCC (4.76 g, 23.12 mmol, 1.1 equiv) was added. After addition the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was then filtered over Celite

[¶¶] This route was only performed on analytical scale.



Scheme 6. Synthesis of extended Horner–Wadsworth–Emmons reagent **11**.

and the residue was washed with CH_2Cl_2 (30 mL). The combined organic extracts were washed with an aq $NaHCO_3$ solution (saturated, 150 mL), H_2O (150 mL), and a saturated brine solution (100 mL), dried and concentrated to a colorless oil. Flash chromatography (Et_2O/pentane 1:99) yielded **S5** as a colorless oil. (*E*)-*S*-Ethyl 4-bromobut-2-enethioate **S5** data in accordance with data described in Ref. 16. [70% yield, colorless oil].

4.1.2.3. Arbuzov reaction of S5. In a round-bottomed flask equipped with stirring bar, (*E*)-*S*-ethyl 4-bromobut-2-enethioate **S5** (2.0 g, 9.57 mmol, 1.0 equiv) and triethyl phosphite (2.33 mL, 13.40 mmol, 1.4 equiv) were mixed and warmed in a preheated oil bath at 100 °C. The mixture was stirred for 30 min and allowed to cool down to room temperature. Flash column chromatography (EtOAc/pentane 67:33) yielded **11** as a light yellow oil. (*E*)-*S*-Ethyl 4-(diethoxyphosphoryl)but-2-enethioate **11**: [65% yield, light yellow oil]. For spectroscopic data vide infra.

4.1.3. Route 3 (Scheme 6)

4.1.3.1. Saponification of triethylphosphonocrotonate S6. Compound **S7** was obtained via a known procedure.[17] 4-Diethoxyphosphorylbut-2-enoic acid **S7** data in accordance with data described in Ref. 17 (4-diethoxyphosphoryl-2-butenoic acid). [70% yield, colorless oil].

4.1.3.2. Thioesterification of S7. In a round-bottomed flask equipped with stirring bar under a N_2 atmosphere, 4-diethoxyphosphorylbut-2-enoic acid **S7** (8.98 g, 40.42 mmol, 1.0 equiv), EtSH (3.0 mL, 40.42 mmol 1.0 equiv), and DMAP (0.49 g, 4.04 mmol, 0.1 equiv) were dissolved in CH_2Cl_2 (100 mL), the solution was cooled to 0 °C, and EDC-HCl salt (8.52 g, 44.46 mmol, 1.1 equiv) was added. After addition the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was then washed with an aq Na_2CO_3 solution (saturated, 3 × 100 mL), H_2O (2 × 100 mL) and a saturated brine solution (75 mL). The organic extracts were dried and carefully concentrated to a colorless oil. Flash column chromatography (gradient EtOAc/pentane 20:80 to EtOAc) yielded **11** as a colorless oil. (*E*)-*S*-Ethyl 4-(diethoxyphosphoryl)but-2-enethioate **11**: [81% yield, colorless oil]. ^{1}H NMR δ 6.85–6.67 (m, 1H), 6.20 (dd, J = 15.5 Hz, 4.8 Hz, 1H), 4.20–3.98 (m, 4H), 2.92 (q, J = 7.4 Hz, 2H), 2.70 (ddd, J = 23.0 Hz, 7.8 Hz, 1.3 Hz, 2H), 1.30 (t, J = 7.1 Hz, 6H), 1.25 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 188.83 (C), 133.03 (d, $^2J_{C\text{-}P}$ 11.2, CH), 132.24 (d, $^3J_{C\text{-}P}$ 13.7, 1H), 62.04 (d, $J_{C\text{-}P}$ 6.6, CH_2), 30.10 (d, $^2J_{C\text{-}P}$ 138.2, CH_2), 22.86 (CH_2), 16.11 (d $^3J_{C\text{-}P}$ 5.9, CH_3), 14.40 (CH_3); ^{31}P NMR δ 25.13 (t, J = 13.6 Hz); MS m/z 266 (M^+, 3), 205 (M−SEt, 62), 177 (M−COSEt, 33), 149 ($C_5H_{10}O_3$, 100); HRMS calcd for $C_{10}H_{19}O_4PS$ 266.0742, found 266.0729.

4.1.3.3. Synthesis of substrates for 1,6-addition. *4.1.3.3.1. Thioesterification of sorbic acid*[18]. In a round-bottomed flask equipped with stirring bar under N_2 atmosphere, sorbic acid (1.12 g, 10.0 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (30 mL). Subsequently, DMAP (0.12 g, 1.0 mmol, 0.1 equiv) and EtSH (0.97 mL, 13.0 mmol, 1.3 equiv) were added and the reaction mixture was cooled to 0 °C using an ice bath. Then, DCC (2.17 g, 10.5 mmol, 1.05 equiv) dissolved in anhydrous CH_2Cl_2 (15 mL) was added slowly. After addition, the ice bath was removed and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was then filtered over Celite and the residue was washed with CH_2Cl_2 (50 mL). The combined organic extracts were then washed with saturated aqueous $NaHCO_3$-solution (50 mL), H_2O (50 mL) and a saturated brine solution (50 mL), dried, and concentrated. Flash column chromatography (Et_2O/pentane 2.5:97.5) yielded **7a** as a colorless oil. (2*E*,4*E*)-*S*-Ethylhexa-2,4-dienethioate **7a**: [80% yield, colorless oil] ^{1}H NMR δ 7.14 (dd, J = 15.2 Hz, 10.1 Hz, 1H), 6.22–6.06 (m, 2H), 6.02 (d, J = 15.1 Hz, 1H), 2.92 (qd, J = 7.4 Hz, 1.3 Hz, 2H), 1.82 (d, J = 5.9 Hz, 3H), 1.24 (td, J = 7.4 Hz, 1.3 Hz, 3H); ^{13}C NMR δ 190.26 (C), 140.99 (CH), 140.85 (CH), 129.84 (CH), 126.39 (CH), 23.31 (CH_2), 19.01 (CH_3), 15.03 (CH_3); MS m/z 156 (M^+, 15), 95 (M−SEt, 100), 67 (M−COSEt, 38); HRMS calcd for $C_8H_{12}OS$ 156.0609, found 156.0607.

4.1.3.4. Wittig reaction of (*E*)-hept-2-enal and *S*-ethyl 2-(triphenylphosphoranylidene)ethanethioate. In a round-bottomed flask equipped with stirring bar, triethyl phosphate *S*-ethyl 2-(triphenylphosphoranylidene)ethanethioate (5.43 g, 14.9 mmol, 1.3 equiv) was dissolved in anhydrous CH_2Cl_2 (80 mL). The (*E*)-hept-2-enal (1.5 mL, 11.5 mmol, 1.0 equiv) was added, then the reaction mixture was heated at reflux, and stirred for 20 h. The reaction mixture was then concentrated and the remaining solid was extracted with *n*-pentane (3 × 10 mL). The combined organic extracts were concentrated to a yellow oil. Flash column chromatography (Et_2O/pentane 1:99) yielded **7b** as a colorless oil. (2*E*,4*E*)-*S*-Ethylnona-2,4-dienethioate **7b**: [61% yield, 14:1 *E*/*Z*-ratio, colorless oil]. ^{1}H NMR δ 7.16 (dd, J = 15.2 Hz, 10.1 Hz, 1H), 6.22–6.09 (m, 2H), 6.05 (d, J = 15.2 Hz, 1H), 2.93 (q, J = 7.4 Hz, 2H), 2.16 (dd, J = 13.9 Hz, 6.7 Hz, 2H), 1.39 (dt, J = 14.4 Hz, 7.2 Hz, 2H), 1.34–1.29 (m, 2H), 1.26 (td, J = 7.4 Hz, 0.5 Hz, 3H), 0.88 (t, J = 7.2 Hz,

3H); ^{13}C NMR δ 190.33 (C), 146.56 (CH), 141.14 (CH), 128.42 (CH), 126.56 (CH), 33.06 (CH_2), 30.99 (CH_2), 23.35 (CH_2), 22.44 (CH_2), 15.08 (CH_3), 14.07 (CH_3); MS *m*/*z* 198 (M^+, 14), 137 (M−SEt, 100), 81 (C_5H_5O, 39); HRMS calcd for $C_{11}H_{18}OS$ 198.1078, found 198.1083; *E*/*Z* ratio was determined by ^{1}H NMR.

4.1.3.5. General procedure for the Horner–Wadsworth–Emmons reaction of an aldehyde and HWE reagent 11. In a round-bottomed flask equipped with stirring bar (*E*)-*S*-ethyl 4-(diethoxyphosphoryl)but-2-enethioate **11** (1.5 equiv) was dissolved in anhydrous THF (20.0 mL/mmol substrate) and cooled to −78 °C. The LHMDS (1 M in THF, Aldrich, 1.4 equiv) was added dropwise and the mixture stirred for 30 min. Then, the aldehyde (1.0 equiv) dissolved in anhydrous THF (4.0 mL/mmol substrate) was added dropwise. After addition, the solution was allowed to warm to −40 °C (in approximately 3 h) and stirred for 16 h in total. A solution of NH_4Cl (1 M, 2 mL/mmol substrate) was added and the mixture was extracted with Et_2O (3 × 4 mL/mmol substrate). The combined organic extracts were dried and concentrated. Flash column chromatography (Et_2O/pentane 1:99) yielded **7** as a colorless oil.

(2*E*,4*E*)-*S*-Ethyl 7-methylocta-2,4-dienethioate **7c**: [70% yield (0.5 mmol scale), >95:5 *E*/*Z*-ratio, colorless oil]. ^{1}H NMR δ 7.16 (d, *J* = 15.2 Hz, 10.0 Hz, 1H), 6.20–6.01 (m, 3H), 2.93 (q, *J* = 7.3 Hz, 2H), 2.03 (t, *J* = 6.6 Hz, 2H), 1.68 (dt, *J* = 13.3 Hz, 6.7 Hz, 1H), 1.25 (t, *J* = 7.4 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR δ 190.29 (C), 145.28 (CH), 141.02 (CH), 129.50 (CH), 126.64 (CH), 42.65 (CH_2), 28.47 (CH), 23.33 (CH_2), 22.52 (CH_3), 15.06 (CH_2); MS *m*/*z* 198 (M^+, 18), 137 (M−SEt, 100); HRMS calcd for $C_{11}H_{18}OS$ 198.1078, found 198.1087; *E*/*Z* ratio was determined by ^{1}H NMR.

(2*E*,4*E*)-*S*-Ethyl 7-phenylhepta-2,4-dienethioate **7d**: [39% yield (0.5 mmol scale), >95:5 *E*/*Z*-ratio, colorless oil]. ^{1}H NMR δ 7.33–7.25 (m, 2H), 7.23–7.13 (m, 4H), 6.25–6.11 (m, 2H), 6.07 (d, *J* = 15.2 Hz, 1H), 2.96 (qd, *J* = 7.4 Hz, 1.1 Hz, 2H), 2.75 (t, *J* = 7.7 Hz, 2H), 2.50 (dd, *J* = 14.5 Hz, 7.0 Hz, 2H), 1.28 (td, *J* = 7.4 Hz, 1.2 Hz, 3H); ^{13}C NMR δ 190.07 (C), 144.80 (CH), 141.10 (C), 140.63 (CH), 128.92 (CH), 128.54 (CH), 128.48 (CH), 126.93 (CH), 126.20 (CH), 35.13 (CH_2), 34.96 (CH_2), 23.28 (CH_2), 14.99 (CH_3); MS *m*/*z* 246 (M^+, 4), 185 (M−SEt, 63), 91 ($C_6H_5CH_2$, 100); HRMS calcd for $C_{15}H_{18}OS$ 246.1078, found 246.1090, *E*/*Z* ratio was determined by ^{1}H NMR.

(2*E*,4*E*)-*S*-Ethyl 6-(benzyloxy)hexa-2,4-dienethioate **7e**:[||||] [47% yield (0.5 mmol scale), >95:5 *E*/*Z*-ratio, colorless oil, purified by flash column chromatography (2:98 to 6:94 Et_2O/pentane)]. ^{1}H NMR δ 7.30–7.15 (m, 5H), 7.09 (dd, *J* = 15.2 Hz, 10.0 Hz, 1H), 6.15–6.01 (m, 2H), 5.98 (d, *J* = 15.1 Hz, 2H), 4.40 (s, 2H), 3.39 (td, *J* = 6.2 Hz, 1.5 Hz, 2H), 2.87 (qd, *J* = 7.4 Hz, 1.7 Hz, 2H), 2.24–2.16 (m, 2H), 1.72–1.61 (m, 2H), 1.19 (td, *J* = 7.4 Hz, 1.8 Hz, 3H); ^{13}C NMR δ 190.11 (C), 145.37 (CH), 140.76 (CH), 138.53 (C), 128.75 (CH), 128.49 (CH), 127.76 (CH), 127.70 (CH), 126.73 (CH), 73.05 (CH_2), 69.40 (CH_2), 29.95 (CH_2), 28.87 (CH_2), 23.27 (CH_2), 15.00 (CH_3); MS *m*/*z* 229 (M^+−SEt, 1), 91 ($C_6H_5CH_2$, 100); HRMS calcd for $C_{17}H_{22}O_2SNa$ 313.1238, found 313.1228; *E*/*Z* ratio was determined by ^{1}H NMR.

4.2. General procedure for the reduction of a thioester to an aldehyde

In a dried Schlenk tube equipped with a septum and a stirring bar under a N_2 atmosphere (*S*)-*S*-ethyl 6-(benzyloxy)-3-methylhexanethioate (0.51 g, 2.21 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (5 mL). After 5 min stirring at room temperature, the mixture was cooled to −75 °C and DIBAL-H (1.0 M solution in CH_2Cl_2, 2.66 mL, 2.66 mmol, 1.2 equiv) was added. The solution turned pink/orange. The reaction mixture was stirred for 5 h at −75 °C. Subsequently the reaction mixture was poured into a round-bottomed flask with aq Rochelle's salt-solution (saturated, 10 mL), stirred for 1 h at rt, and the layers were separated. After extraction with CH_2Cl_2 (2 × 5 mL), the combined organic extracts were washed with the aq Rochelle's salt solution (2 × 5 mL), dried, and carefully concentrated. The aldehyde was used without further purification in the subsequent HWE reaction.

4.2.1. Chain extension

Compounds **7f** and **19** were obtained via the general procedure for the Horner–Wadsworth–Emmons reaction of the corresponding aldehyde and HWE reagent **11**.

4.2.1.1. (*S*,2*E*,4*E*)-*S*-Ethyl 10-(benzyloxy)-7-methyldeca-2,4-dienethioate 7f[†††,‡‡‡]**.** Compound **7f** [64% yield (two steps, 0.5 mmol scale), >95:5 *E*/*Z*-ratio, $[\alpha]_D^{20} = +1.2$ (*c* 1.0, $CHCl_3$), colorless oil]. ^{1}H NMR δ 7.30–7.17 (m, 5H), 7.12 (dd, *J* = 15.2 Hz, 9.6 Hz, 1H), 6.14–5.96 (m, 3H), 4.42 (s, 2H), 3.37 (t, *J* = 6.6 Hz, 2H), 2.88 (q, *J* = 7.4 Hz, 2H), 2.16–2.06 (m, 1H), 2.00–1.90 (m, 1H), 1.66–1.44 (m, 3H), 1.39–1.27 (m, 1H), 1.25–1.07 (m, 4H), 0.82 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR δ 190.13 (C), 144.91 (CH), 140.83 (CH), 138.70 (C), 129.63 (CH), 128.47 (CH), 127.72 (CH), 127.63 (CH), 126.59 (CH), 73.02 (CH_2), 70.66 (CH_2), 40.71 (CH_2), 33.12 (CH), 33.01 (CH_2), 27.43 (CH_2), 23.27 (CH_2), 19.65 (CH_3), 15.03 (CH_3); MS *m*/*z* 332 (M^+, 1), 91 ($C_6H_5CH_2$, 100); HRMS calcd for $C_{20}H_{28}O_2SNa$ 355.1708, found 355.1699; *E*/*Z* ratio was determined by ^{1}H NMR.

4.2.1.2. (2*E*,4*E*,7*S*,9*S*)-*S*-Ethyl 7,9-dimethyltrideca-2,4-dienethioate 19. Compound **19** [61% yield (two steps), >95:5 *E*/*Z*-ratio, $[\alpha]_D^{20} = +9.4$ (*c* 1.0, $CHCl_3$), colorless oil]. ^{1}H NMR δ 7.19 (dd, *J* = 15.1 Hz, 9.9 Hz, 1H), 6.23–6.02 (m, 3H), 2.95 (q, *J* = 7.4 Hz, 2H), 2.23–2.14 (m, 1H), 1.96 (dt, *J* = 14.5 Hz, 7.3 Hz, 1H), 1.72–1.61 (m, 1H), 1.53–1.41 (m, 1H), 1.33–1.15 (m, 9H), 1.11–1.00 (m, 1H), 1.00–0.91 (m, 1H), 0.91–0.78 (m, 9H); ^{13}C NMR δ 190.24 (C), 145.23 (CH), 140.95 (CH), 129.60 (CH), 126.48 (CH), 44.71 (CH_2), 40.56 (CH_2), 36.59 (CH_2), 30.47 (CH), 30.12 (CH), 29.28 (CH_2), 23.28 (CH_2), 23.16 (CH_2), 20.31 (2 × CH_3), 15.00 (CH_3), 14.30 (CH_3); MS *m*/*z* 253 (M^+−Et, 1), 109 (C_7H_9O,55), 95 (C_6H_7O, 100), 81 (C_5H_5O, 100), 55 (C_3H_3O, 74); HRMS calcd for $C_{17}H_{31}OS$ 283.2096, found 283.2090.

4.3. General procedure for the enantioselective 1,6-conjugate addition:[7,§§§] (exemplified for the addition of MeMgBr to 7b)

In a dried Schlenk tube equipped with a septum and a stirring bar under a N_2 atmosphere, $CuBr{\cdot}SMe_2$ (5.14 mg, 25 μmol, 5.0 mol %) and (*S*,*R*)-reversed Josiphos (15.46 mg, 26 μmol,

[||||] The required aldehyde was prepared *via* known procedures. Synthesis of 4-benzyloxybutane-1-ol is described in van Summeren, R. P.; Moody, D. B.; Feringa, B. L.; Minnaard, A. J.; *J. Am. Chem. Soc.* **2006**, *128*, 4546-4547. Subsequent oxidation to the aldehyde was performed using IBX oxidation described in Harutyunyan, S. R.; Zhao, Z.; den Hartog, T.; Bouwmeester, K.; Minnaard, A. J.; Feringa, B. L.; Govers, F. *Proc Natl. Acad. Sci. USA* **2008**, *105*, 8507-8512 (4-(*tert*-butyldimethylsilanyloxy)but-2-enethioic acid S-ethyl ester).

[†††] The required aldehyde was prepared as described in ||||. Then subsequent Wittig olefination and asymmetric 1,4-addition were described in van Summeren, R. P.; Moody, D. B.; Feringa, B. L.; Minnaard, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 4546-4547. Finally, reduction to the aldehyde is described in ref 6f ((-)-(5***R***,7***R***,9***S***,11***S***,13***S***) -14-(*tert*-butyl-diphenyl-silanyloxy)-5,7,9,11,13-pentamethyl-tetradec-2-enethioic acid S-ethyl ester).

[‡‡‡] Enantiomeric excess and regioselectivity for (*S*)-S-ethyl 6-(benzyloxy)-3-methylhexanethioate were determined by chiral HPLC analysis, column: Chiralcel-OB-H, (99.5:0.5 heptane:***i***PrOH); retention times (min): 28.5 ((*S*)-enantiomer), 29.7 ((*R*)-enantiomer).

[§§§] This reaction has been performed up to 2.7 mmol scale. For reactions at a larger scale extended reaction times are required. Typically >95% conversion was achieved in up to 40 h.

5.25 mol %) were dissolved in anhydrous CH_2Cl_2 (2 mL). After 5 min stirring at room temperature, the mixture was cooled to −70 °C and MeMgBr (Aldrich, 3.0 M solution in Et_2O, 0.33 mL, 1.0 mmol, 2.0 equiv) was added. After stirring for an additional 10 min, a solution of **7b** (70.1 mg, 0.5 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (additional 0.5 mL) was added with syringe pump over 2 h. The reaction mixture was stirred overnight (16 h including addition) at −70 °C and subsequently EtOH (0.1 mL) and an aq NH_4Cl-solution (1 M, 0.5 mL) were added. The mixture was warmed to room temperature and an additional 5 mL of the NH_4Cl-solution and 5 mL of CH_2Cl_2 were added and the layers were separated. After extraction with CH_2Cl_2 (2 × 5 mL), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (Et_2O/pentane 1:99) yielded **13b** as a colorless[¶¶¶] oil.

4.3.1. (*S,E*)-*S*-Ethyl 5-methylnon-3-enethioate 13b

Compound **13b** [83% yield, 89% ee, 99:1 regioselectivity (1,6:1,4), $[\alpha]_D^{20} = +9.0$ (*c* 1.0, $CHCl_3$), colorless oil]. ^{1}H NMR δ 5.50–5.39 (m, 2H), 3.19 (d, *J* = 5.7 Hz, 2H), 2.84 (q, *J* = 7.4 Hz, 2H), 2.18–2.04 (m, 1H), 1.31–1.16 (m, 9H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.86 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR δ 198.74 (C), 142.55 (CH), 119.57 (CH), 47.89 (CH_2), 36.94 (CH), 36.73 (CH_2), 29.70 (CH_2), 23.50 (CH_2), 22.98 (CH_2), 20.55 (CH_3), 14.90 (CH_3), 14.33 (CH_3); MS *m*/*z* 214 (M^+, 10), 124 (M−SEt-Et, 34), 83 (C_6H_{11}, 46), 69 (C_5H_9, 100); HRMS calcd for $C_{12}H_{22}OS$ 214.1391, found 214.1401.

Enantiomeric excess and regioselectivity were determined by chiral GC analysis, column: Chiraldex-B-PM, 50–98 °C in 4.8 min, 98 °C for 200 min; retention times (min): 163.8 (an enantiomer of the 1,4-addition product), 191.1 ((*R*)-enantiomer), 192.3 ((*S*)-enantiomer).

4.3.2. (*S,E*)-*S*-Ethyl 5,7-dimethyloct-3-enethioate 13c

Compound **13c** [84% yield, 82% ee, 95:5 regioselectivity (1,6:1,4), $[\alpha]_D^{20} = +8.3$ (*c* 1.0, $CHCl_3$), colorless oil]. ^{1}H NMR δ 5.51–5.37 (m, 2H), 3.18 (d, *J* = 5.6 Hz, 2H), 2.84 (q, *J* = 7 .4 Hz, 2H), 2.26–2.14 (m, 1H), 1.63–1.50 (m, 1H), 1.32–1.11 (m, 5H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR δ 198.69 (C), 142.58 (CH), 119.48 (CH), 47.87 (CH_2), 46.45 (CH_2), 34.77 (CH), 25.63 (CH), 23.50 (CH_2), 23.21 (CH_3), 22.56 (CH_3), 20.93 (CH_3), 14.92 (CH_3); MS *m*/*z* 214 (M^+, 1), 89 (C_3H_5OS, 24), 83 (C_6H_{11}, 29), 69 (C_4H_5O, 100), 55 (C_3H_3O, 32); HRMS calcd for $C_{12}H_{22}OSNa$ 237.1289, found 237.1280.

Enantiomeric excess was determined by chiral GC analysis, column: Chiraldex-B-PM, 50–80 °C in 3 min, 80 °C for 40 min, 80–160 °C in 8 min, 160 °C for 4 min; for 2,4-dimethylpentanoic acid;[19] retention times (min): 53.7 ((*S*)-enantiomer), 54.0 ((*R*)-enantiomer). Regioselectivity was determined by ^{1}H NMR with 10 s d1-time.

4.3.3. (*S,E*)-*S*-Ethyl 5-methyl-7-phenylhept-3-enethioate 13d

Compound **13d** [78% yield, 82% ee, 99:1 regioselectivity (1,6:1,4), $[\alpha]_D^{20} = +4.1$ (*c* 1.0, $CHCl_3$), colorless oil]. ^{1}H NMR δ 7.33–7.16 (m, 5H), 5.62–5.46 (m, 2H), 3.26 (d, *J* = 5.5 Hz, 2H), 2.90 (q, *J* = 7.4 Hz, 2H), 2.75–2.51 (m, 2H), 2.28–2.15 (m, 1H), 1.72–1.60 (m, 2H), 1.27 (t, *J* = 7.4 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR δ 198.22 (C), 142.69 (C), 141.78 (CH), 128.50 (CH), 128.36 (CH), 125.72 (CH), 120.35 (CH), 47.74 (CH_2), 38.68 (CH_2), 36.50 (CH), 33.69 (CH_2), 23.41 (CH_2), 20.57 (CH_3), 14.85 (CH_3); MS *m*/*z* 262 (M^+, 1), 200 (M^+−SEtH, 16), 131 ($C_{10}H_{11}$, 40), 117 (C_5H_9OS, 15), 104 (C_4H_8OS, 20), 91 ($C_6H_5CH_2$, 100); HRMS calcd for $C_{16}H_{24}OS$ 263.1470, found 263.1464.

[¶¶¶] Occasionally the product was polluted with a yellow coloured side product undetectable by GC/MS or NMR.

Enantiomeric excess and regioselectivity were determined by chiral HPLC analysis, column: Chiralcel-OB-H, (99:1 heptane/*i*PrOH); retention times (min): 14.7 (1,4-addition product), 19.6 ((*S*)-enantiomer), 17.9 ((*R*)-enantiomer).

4.3.4. (*S,E*)-*S*-Ethyl 8-(benzyloxy)-5-methyloct-3-enethioate 13e

This product was purified with flash chromatography (gradient 1:99 to 5:95 Et_2O/pentane). [86% yield, 86% ee, 94:6 regioselectivity (1,6:1,4), $[\alpha]_D^{20} = +5.9$ (*c* 1.0, $CHCl_3$), colorless oil]. ^{1}H NMR δ 7.36–7.24 (m, 5H), 5.54–5.41 (m, 2H), 4.49 (s, 2H), 3.45 (t, *J* = 6.6 Hz, 2H), 3.20 (dd, *J* = 3.9 Hz, 1.6 Hz, 2H), 2.85 (q, *J* = 7.4 Hz, 2H), 2.20–2.09 (m, 1H), 1.70–1.52 (m, 2H), 1.45–1.30 (m, 2H), 1.23 (t, *J* = 7.4 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H).; ^{13}C NMR δ 198.37 (C), 141.91 (CH), 138.78 (C), 128.45 (CH), 127.71 (CH), 127.58 (CH), 119.97 (CH), 72.95 (CH_2), 70.57 (CH_2), 47.73 (CH_2), 36.80 (CH), 33.34 (CH_2), 27.66 (CH_2), 23.42 (CH_2), 20.51 (CH_3), 14.85 (CH_3); MS *m*/*z* 277 (M^+−Et, 1), 153 ($C_9H_{13}O_2$, 14), 91 ($C_6H_5CH_2$, 100); HRMS calcd for $C_{18}H_{26}O_2SNa$ 329.1551, found 329.1538.

Enantiomeric excess was determined by chiral HPLC analysis, column: Chiralcel-OJ-H, (98:2 heptane/*i*PrOH); for (*E*)-methyl 8-(benzyloxy)-5-methyloct-3-enoate;[|||||||] retention times (min): 23.5 ((*S*)-enantiomer), 24.7 ((*R*)-enantiomer). Regioselectivity was determined by ^{1}H NMR with 10 s d1-time.

4.3.5. *Syn*-selective enantioselective 1,6-addition

4.3.5.1. (5*S*,7*S*,*E*)-*S*-Ethyl 10-(benzyloxy)-5,7-dimethyldec-3-enethioate 13f. Compound **13f** [88% yield, 87% *syn*-product (**13f**) and 13% of *anti*-product (**13g**), 85:15 regioselectivity (1,6:1,4), $[\alpha]_D^{20} = -0.9$ (*c* 1.0, $CHCl_3$), colorless oil]. ^{1}H NMR δ 7.38–7.23 (m, 5H), 5.52–5.25 (m, 2H), 4.50 (s, 2H), 3.44 (t, *J* = 6.7 Hz, 2H), 3.19 (d, *J* = 6.4 Hz, 2H), 2.86 (q, *J* = 7.4 Hz, 2H), 2.32–2.19 (m, 1H), 1.72–1.01 (m, 10H), 1.00–0.92 (m, 3H), 0.89–0.79 (m, 3H); residual peaks 1,4-addition product: 2.75–2.64 (m, 1H), 2.50 (ddd, *J* = 36.1, 14.4, 7.3 Hz, 2H), residual peaks α,β-unsaturated 1,6-addition product: 2.04–1.76 (m, 1H); ^{13}C NMR δ 198.55 (C), 142.21 (CH), 138.81 (C), 128.47 (CH), 127.73 (CH), 127.59 (CH), 119.73 (CH), 72.99 (CH_2), 70.96 (CH_2), 47.76 (CH_2), 44.51 (CH_2), 34.59 (CH), 33.93 (CH_2), 30.25 (CH), 27.34 (CH_2), 23.40 (CH_2), 21.43 (CH_3), 19.50 (CH_3), 14.93 (CH_3); residual peaks *anti*-product: 198.68 (C), 142.71 (CH), 119.28 (CH), 44.37 (CH_2), 34.31 (CH), 33.22 (CH_2), 30.16 (CH), 20.30 (CH_3), 19.91 (CH_3), 14.83 (CH_3); residual peaks 1,4-addition product of the 1,6-ACA: 135.20, 128.16, 54.33, 51.35, 44.88, 42.91, 39.91, 33.09, 32.92, 21.71, 20.41; MS *m*/*z* 319 (M^+−Et, 1), 91 ($C_6H_5CH_2$, 100); HRMS calcd for $C_{21}H_{32}O_2SNa$ 371.2021, found 371.2010.

Ratio of *syn*- and *anti*-product was determined by ^{13}C NMR with 10 s d1-time. Regioselectivity was determined by ^{1}H NMR with 10 s d1-time.

4.3.5.2. (5*S*,7*S*,9*S*,*E*)-*S*-Ethyl 5,7,9-trimethyltridec-3-enethioate 20. Compound **20** [87% yield, 91% *syn*-product **20** and 9% of *anti*-product **21**, 90:10 regioselectivity (1,6:1,4), $[\alpha]_D^{20} = -2.4$ (*c* 1.0, $CHCl_3$), colorless oil]. ^{1}H NMR δ 5.53–5.25 (m, 2H), 3.20 (d, *J* = 6.6 Hz, 2H), 2.90–2.81 (m, 2H), 2.26 (dt, *J* = 13.6 Hz, 6.7 Hz, 14H), 1.61–1.39 (m, 3H), 1.34–1.10 (m, 10H), 1.06–0.74 (m, 14H); residual peaks 1,4-addition product of the 1,6-ACA: 2.69

[|||||||] (*E*)-methyl 8-(benzyloxy)-5-methyloct-3-enoate was obtained via the following procedure; The substrate (~10 mg) was dissolved in MeOH (0.5 mL) and stirred for 3 h in the presence of K_2CO_3 (excess), then an aq. NH_4Cl-solution (1 M, 0.5 mL) was added and the layers were separated. After extraction with Et_2O (2x 0.5 mL), the combined organic extracts were dried and carefully concentrated to a yellow oil. Filtration over a short SiO_2-column (eluent Et_2O) and evaporation of the solvent yielded the product as a colorless oil.

(dd, J = 13.9 Hz, 7.0 Hz, 1H), 2.50 (ddd, J = 38.1 Hz, 14.4 Hz, 7.3 Hz, 2H). residual peaks α,β-unsaturated 1,6-ACA product: 1.97 (dd, J = 12.7 Hz, 7.0 Hz, 2H), 1.79–1.69 (m, 2H); ^{13}C NMR δ 198.59 (C), 142.32 (CH), 119.76 (CH), 47.80 (CH_2), 45.82 (CH_2), 44.54 (CH_2), 36.76 (CH_2), 34.63 (CH), 30.00 (CH), 29.35 (CH_2), 27.72 (CH_2), 23.42 (CH), 23.20 (CH_2), 21.64 (CH_3), 20.33 (2 × CH_3), 14.84 (CH_3), 14.34 (CH_3); residual peaks 1,4-addition product of the 1,6-ACA: 51.40, 39.66, 30.49; MS m/z 269 (M^+−Et, 1), 111 ($C_7H_{11}O$, 57), 97 (C_6H_9O,55), 69 (C_4H_5O, 100), 57 (C_4H_9, 75), 55 (C_3H_3O, 62); HRMS calcd for $C_{18}H_{34}OSNa$ 321.2228, found 321.2217.

Ratio of *syn*- and *anti*-product was determined by ^{13}C NMR with 10 s d1-time. Regioselectivity was determined by ^{1}H NMR with 10 s d1-time.

4.3.6. *Anti*-selective enantioselective 1,6-addition

4.3.6.1. (5*R*,7*S*,*E*)-*S*-Ethyl 10-(benzyloxy)-5,7-dimethyldec-3-enethioate 13g. Compound **13g** [83% yield, 78% *anti*-product (**13g**) and 22% of *syn*-product (**13f**), 87:13 regioselectivity (1,6:1,4), $[\alpha]_D^{20} = -2.2$ (c 1.0, $CHCl_3$), colorless oil]. ^{1}H NMR δ 7.38–7.24 (m, 5H), 5.53–5.25 (m, 2H), 4.51 (s, 2H), 3.50–3.40 (m, 2H), 3.24–3.15 (m, 2H), 2.86 (qd, J = 7.4 Hz, 1.4 Hz, 2H), 2.32–2.19 (m, 4H), 1.74–1.09 (m, 10H), 0.96 (dd, J = 9.0 Hz, 6.7 Hz, 3H), 0.90–0.77 (m, 3H); residual peaks 1,4-addition product of the 1,6-ACA: 2.70 (dd, J = 13.8 Hz, 6.7 Hz, 1H), 2.50 (ddd, J = 35.0 Hz, 14.3 Hz, 7.2 Hz, 2H); residual peaks α,β-unsaturated 1,6-ACA product: 2.05–1.95 (m, 1H), 1.86–1.75 (m, 1H), 1.02 (d, J = 6.7 Hz, 3H); ^{13}C NMR δ 198.55 (C), 142.72 (CH), 138.81 (C), 128.46 (CH), 127.73 (CH), 127.59 (CH), 119.28 (CH), 72.99 (CH_2), 71.01 (CH_2), 47.77 (CH_2), 44.37 (CH_2), 34.31 (CH), 33.23 (CH_2), 30.17 (CH), 27.24 (CH_2), 23.42 (CH_2), 20.31 (CH_3), 19.91 (CH_3), 14.83 (CH_3); residual peaks *syn*-product: 142.22 (CH), 119.73 (CH), 44.51 (CH_2), 34.59 (CH), 33.93 (CH_2), 30.25 (CH), 27.35 (CH_2), 21.44 (CH_3), 19.51 (CH_3), 14.93 (CH_3); residual peaks 1,4-addition product of the 1,6-ACA: 135.18, 128.27, 51.37, 39.96, 33.05, 32.97, 27.45, 20.45; MS m/z 319 (M^+−Et, 1), 91 ($C_6H_5CH_2$, 100); HRMS calcd for $C_{21}H_{32}O_2SNa$ 371.2021, found 371.2010.

Ratio of *syn*- and *anti*-product was determined by ^{13}C NMR with 10 s d1-time. Regioselectivity was determined by ^{1}H NMR with 10 s d1-time.

4.3.6.2. (5*R*,7*S*,9*S*,*E*)-*S*-Ethyl 5,7,9-trimethyltridec-3-enethioate 21. Compound **21** [85% yield, 72% *anti*-product **21** and 28% of *syn*-product **20**, 90:10 regioselectivity (1,6:1,4), $[\alpha]_D^{20} = +2.5$ (c 1.0, CH_2Cl_2), colorless oil]. ^{1}H NMR δ 5.54–5.24 (m, 2H), 3.23–3.11 (m, 2H), 2.92–2.77 (m, 2H), 2.33–2.17 (m, 1H), 1.59–1.38 (m, 3H), 1.33–1.12 (m, 10H), 1.08–0.64 (m, 14H); residual peaks 1,4-addition product of the 1,6-ACA: 2.77–2.64 (m, 1H), 2.50 (ddd, J = 37.7 Hz, 14.4 Hz, 7.3 Hz, 1H); residual peaks α,β-unsaturated 1,6-ACA product: 2.03–1.93 (m, 1H), 1.78–1.67 (m, 1H); ^{13}C NMR δ 198.72 (C), 142.95 (CH), 119.13 (CH), 47.81 (CH_2), 45.48 (CH_2), 44.56 (CH_2), 36.51 (CH_2), 34.26 (CH), 30.07 (CH), 29.31 (CH_2), 27.68 (CH_2), 23.43 (CH), 23.21 (CH_2), 20.60 (CH_3), 20.50 (CH_3), 20.46 (CH_3), 20.10 (CH_3), 14.34 (CH_3); residual peaks *syn*-product: 198.55 (C), 142.32 (CH), 119.76 (CH), 45.82 (CH_2), 44.70 (CH_2), 36.75 (CH_2), 34.63 (CH), 30.45 (CH), 21.64 (CH_3), 20.33 (CH_3), 14.84 (CH_3); residual peaks 1,4-addition product of the 1,6-ACA: 135.09, 128.40, 51.41, 39.80, 36.70, 34.51, 20.16, 14.93; MS m/z 269 (M^+−Et, 1), 111 ($C_7H_{11}O$, 57), 97 (C_6H_9O,55), 69 (C_4H_5O, 100), 57 (C_4H_9, 75), 55 (C_3H_3O, 62); HRMS calcd for $C_{18}H_{35}OS$ 299.2403, found 299.2404.

Ratio of *syn*- and *anti*-product was determined by ^{13}C NMR with 10 s d1-time. Regioselectivity was determined by ^{1}H NMR with 10 s d1-time.

4.4. General procedure for the isomerization of the β,γ-unsaturated thioester to the α,β-unsaturated thioester:[††††] (exemplified for the isomerization of 13b)

In a dried round-bottomed flask equipped with a cooler and a stirring bar under a N_2 atmosphere, **13b** (0.37 g, 1.7 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (18 mL). After 5 min stirring at room temperature DBU (1.3 mL, 8.6 mmol, 5.0 equiv) was added and the reaction mixture immediately turned yellow/orange. The reaction mixture was heated at reflux and stirred for 16 h. Subsequently an aq NH_4Cl-solution (1 M, 20 mL) and 10 mL of CH_2Cl_2 were added and the layers were separated. After extraction with CH_2Cl_2 (2 × 10 mL), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (Et_2O/pentane 1:99) yielded **15b** as a colorless oil.

4.4.1. (*S*,*E*)-*S*-Ethyl 5-methylnon-2-enethioate 13b

Data are in accordance with data described in Ref. 4d. [91% yield of a mixture of 88% α,β-, 12% β,γ-unsaturated 1,6-ACA product and traces of 1,4-addition side product from the 1,6-ACA, $[\alpha]_D^{20} = +1.0$ (c 1.0, $CHCl_3$), literature value[4d]: $[\alpha]_D = -2.0$ (c 1.0, $CHCl_3$) for (*S*)-enantiomer, colorless oil]. Ratio of α,β- and β,γ-product was determined by ^{1}H NMR with 10 s d1-time.

4.4.2. (*S*,*E*)-*S*-Ethyl 5,7-dimethyloct-2-enethioate 13c

Compound **13c** [87% yield of a mixture of 90% α,β-, 10% β,γ-unsaturated 1,6-ACA product and traces of 1,4-addition side product from the 1,6-ACA, $[\alpha]_D^{20} = -4.3$ (c 1.0, $CHCl_3$), colorless oil]. ^{1}H NMR δ 6.86 (dt, J = 15.2 Hz, 7.5 Hz, 1H), 6.08 (dt, J = 15.4 Hz, 1.4 Hz, 1H), 2.93 (q, J = 7.4 Hz, 2H), 2.24–2.11 (m, 1H), 2.05–1.92 (m, 1H), 1.77–1.51 (m, 2H), 1.33–0.77 (m, 14H); residual peaks β,γ-unsaturated 1,6-ACA product and 1,4-addition product of the 1,6-ACA: 5.49–5.23 (m), 3.19 (d), 2.89–2.80 (m), 2.74–2.65 (m), 2.53 (dd), 2.48–2.41 (m), 1.84 (t); ^{13}C NMR δ 190.14 (C), 144.34 (CH), 129.90 (CH), 46.37 (CH_2), 40.07 (CH_2), 30.31 (CH), 25.34 (CH), 23.37 (CH_3), 23.16 (CH_2), 22.27 (CH_3), 19.77 (CH_3), 14.95 (CH_3); residual peaks β,γ-unsaturated 1,6-ACA product and 1,4-addition side product from 1,6-ACA: 142.47, 134.92, 128.62, 119.40, 51.38, 47.78, 41.94, 34.68, 34.51, 28.48, 25.54, 22.47, 22.36, 22.32, 20.84, 20.46; MS m/z 214 (M^+, 1), 153 (M^+−SEt, 46), 83 (C_6H_{11}, 39), 55 (C_3H_3O, 64); HRMS calcd for $C_{12}H_{22}OSNa$ 237.1289, found 237.1279.

Ratio of α,β- and β,γ-product was determined by ^{1}H NMR with 10 s d1-time.

4.4.3. (*S*,*E*)-*S*-Ethyl 5-methyl-7-phenylhept-2-enethioate 13d

This reaction was performed at room temperature. Reaction at reflux gave lower yield and a side-product. [87% yield of a mixture of 89% α,β-, 11% β,γ-unsaturated 1,6-ACA product and traces of 1,4-addition side product from the 1,6-ACA, 80% ee, $[\alpha]_D^{20} = +3.9$ (c 1.0, $CHCl_3$), colorless oil]. ^{1}H NMR δ 7.33–7.22 (m, 2H), 7.21–7.12 (m, 3H), 6.86 (dt, J = 15.3 Hz, 7.5 Hz, 1H), 6.09 (d, J = 15.5 Hz, 1H), 2.94 (q, J = 7.4 Hz, 2H), 2.79–2.46 (m, 2H), 2.30–2.00 (m, 2H), 1.76–1.59 (m, 2H), 1.55–1.41 (m, 1H), 1.28 (td, J = 7.4 Hz, 1.8 Hz, 3H), 0.97 (d, J = 6.5 Hz, 3H); ^{13}C NMR δ 190.05 (C), 143.85 (CH), 142.44 (C), 130.03 (CH), 128.46 (CH), 128.42 (CH), 125.85 (CH), 39.63 (CH_2), 38.56 (CH_2), 33.48 (CH_2), 32.27 (CH_2), 23.16 (CH), 19.61 (CH_3), 14.93 (CH_3); MS m/z 262 (M^+, 1), 105 (C_8H_9, 17), 91 ($C_6H_5CH_2$, 100); HRMS calcd for $C_{16}H_{23}OS$ 263.1470, found 263.1464.

Enantiomeric excess was determined by chiral HPLC analysis, column: Chiralcel-OB-H, (99:1 heptane/*i*PrOH); retention times (min): 16.6 ((*S*)-enantiomer β,γ-unsaturated 1,6-ACA product),

[††††] This reaction was performed from 0.3 mmol up to 1.7 mmol scale.

17.8 ((*R*)-enantiomer β,γ-unsaturated 1,6-ACA product), 19.9 ((*S*)-enantiomer α,β-unsaturated 1,6-ACA product), 24.8 ((*R*)-enantiomer α,β-unsaturated 1,6-ACA product). Ratio of α,β- and β,γ-product was determined by ^{1}H NMR with 10 s d1-time.

4.4.4. (*S*,*E*)-*S*-Ethyl 8-(benzyloxy)-5-methyloct-2-enethioate 13e

This product was purified with flash chromatography (gradient 1:99 to 5:95 Et_2O/pentane). [86% yield of a mixture of 89% α,β-, 11% β,γ-unsaturated 1,6-ACA product and traces of 1,4-addition side product from the 1,6-ACA, $[\alpha]_D^{20} = -1.6$ (*c* 1.0, $CHCl_3$), colorless oil]. ^{1}H NMR δ 7.35–7.19 (m, 5H), 6.82 (dt, *J* = 15.3 Hz, 7.5 Hz, 1H), 6.05 (d, *J* = 15.5 Hz, 1H), 4.45 (s, 2H), 3.41 (t, *J* = 6.6 Hz, 3H), 2.90 (q, *J* = 7.4 Hz, 2H), 2.20–2.10 (m, 1H), 2.04–1.94 (m, 1H), 1.68–1.48 (m, 2H), 1.43–1.29 (m, 2H), 1.27–1.20 (m, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); residual peaks β,γ-unsaturated 1,6-ACA product: 5.46–5.41 (m, 2H), 3.16 (d, *J* = 5.6 Hz, 3H), 2.81 (q, *J* = 7.4 Hz, 2H) 1.20–1.15 (m, 3H), 0.96 (dd, *J* = 6.7 Hz, 3.5 Hz, 3H); ^{13}C NMR δ 190.01 (C), 144.01 (CH), 138.63 (C), 129.93 (CH), 128.42 (CH), 127.69 (CH), 127.57 (CH), 72.98 (CH_2), 70.52 (CH_2), 39.64 (CH_2), 33.14 (CH), 32.56 (CH_2), 27.36 (CH_2), 23.11 (CH_2), 19.61 (CH_3), 14.91 (CH_3); residual peaks β,γ-unsaturated 1,6-ACA product: 141.86 (CH), 119.91 (CH), 69.66 (CH_2), 51.23 (CH_2), 47.68 (CH_2), 36.75 (CH), 33.29 (CH_2), 27.60 (CH_2), 20.45 (CH_3); MS *m*/*z* 277 (M^+−Et, 1), 91 ($C_6H_5CH_2$, 100); HRMS calcd for $C_{18}H_{26}O_2SNa$ 329.1551, found 329.1540.

Ratio of α,β- and β,γ-product was determined by ^{1}H NMR with 10 s d1-time.

4.5. General procedure for the enantioselective 1,4-conjugate addition:[4d,‡‡‡‡] (exemplified for the addition of MeMgBr to 15b)

In a dried Schlenk tube equipped with a septum and a stirring bar under a N_2 atmosphere, the preprepared[4d] Josiphos-complex (5.54 mg, 7.5 μmol, 1.0 mol %) was dissolved in anhydrous *t*BuOMe (3.05 mL). After 5 min stirring at room temperature the mixture was cooled to −78 °C and MeMgBr (Aldrich, 3.0 M solution in Et_2O, 0.38 mL, 1.1 mmol, 1.5 equiv) was added. After stirring for an additional 10 min, a solution of **15b** (0.16 mg, 0.75 mmol, 1.0 equiv) in anhydrous *t*BuOMe (additional 0.75 mL) was added with a syringe pump over 0.5 h. The reaction mixture was stirred overnight (16 h including addition) at −78 °C and subsequently EtOH (0.1 mL) and an aq NH_4Cl-solution (1 M, 0.5 mL) were added. The mixture was warmed to room temperature and an additional 5 mL of the NH_4Cl-solution and 5 mL of Et_2O were added and the layers were separated. After extraction with Et_2O (2 × 5 mL), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (Et_2O/pentane 1:99) yielded **16** as a colorless oil.

4.5.1. (3*S*,5*S*)-*S*-Ethyl 3,5-dimethylnonanethioate is in accordance with data described in Ref. 4d

[83% yield of a mixture of 96% *syn*-product **16** and 4% of *anti*-product **17**, 92% ee, $[\alpha]_D^{20} = -1.3$ (*c* 1.0, $CHCl_3$), literature value:[4d] $[\alpha]_D$ = +2.3 (*c* 0.5, $CHCl_3$) for (*R*,*R*)-enantiomer, colorless oil]. Ratio of *syn*- and *anti*-product and enantiomeric excess were determined by chiral GC analysis as described previously in Ref. 4d, column: Chiralsil-Dex-CB, 50–80 °C in 3 min, 80 °C for 90 min, 80–140 °C in 60 min, retention times (min): 140.2 ((3*S*,5*S*)-enantiomer), 142.1 ((3*S*,5*R*)-enantiomer), 142.5 ((3*R*,5*S*))-enantiomer).

4.5.2. (3*R*,5*S*)-*S*-Ethyl 3,5-dimethylnonanethioate in accordance with data described in Ref. 4d

[77% yield of a mixture of 92% *anti*-product (**17**) and 8% of *syn*-product (**16**), 85% ee, $[\alpha]_D^{20} = +13.9$ (*c* 1.0, $CHCl_3$), literature value:[4d] $[\alpha]_D$ = −8.9 (*c* 0.5, $CHCl_3$) for (3*S*,5*R*)-enantiomer, colorless oil]. Ratio of *syn*- and *anti*-product and enantiomeric excess were determined by chiral GC analysis as described previously in Ref. 4d, column: Chiralsil-Dex-CB, 50–80 °C in 3 min, 80 °C for 90 min, 80–140 °C in 60 min, retention times (min): 140.3 ((3*S*,5*S*)-enantiomer), 140.9 ((3*R*,5*R*)-enantiomer), 142.1 ((3*S*,5*R*)-enantiomer), 142.5 ((3*R*,5*S*))-enantiomer).

4.5.3. (3*S*,5*S*)-*S*-Ethyl 3,5,7-trimethyloctanethioate 22c

Compound **22c** [67% yield of a mixture of 90% *syn*-**22c** and 10% of *anti*-**22c**, $[\alpha]_D^{20} = -9.1$ (*c* 1.0, CH_2Cl_2), colorless oil]. ^{1}H NMR δ 2.87 (q, *J* = 7.4 Hz, 2H), 2.53 (dd, *J* = 14.3 Hz, 5.3 Hz, 1H), 2.28 (dd, *J* = 14.3 Hz, 8.5 Hz, 1H), 2.18–2.07 (m, 1H), 1.70–1.47 (m, 2H), 1.29–1.17 (m, 4H), 1.14–1.06 (m, 1H), 1.05–0.79 (m, 14H); ^{13}C NMR δ 199.51 (C), 51.44 (CH_2), 46.59 (CH_2), 45.24 (CH_2), 28.71 (CH), 27.75 (CH), 25.29 (CH), 23.79 (CH_3), 23.43 (CH_2), 22.17 (CH_3), 20.31 (CH_3), 20.28 (CH_3), 14.98 (CH_3); residual peaks *anti*-product: 47.49, 44.60, 30.47, 22.52, 19.38; MS *m*/*z* 201 (M^+−Et, 4), 112 (M^+−SEt-$(CH_3)_2CHCH_2$, 31), 95 (C_6H_7O, 95), 69 (C_4H_5O, 100), 57 (C_4H_9, 55), 55 (C_3H_3O, 37); HRMS calcd for $C_{13}H_{27}OS$ 231.1777, found 231.1777.

Ratio of *syn*- and *anti*-product was determined by ^{13}C NMR with 10 s d1-time.

4.5.4. (3*S*,5*S*)-*S*-Ethyl 3,5-dimethyl-7-phenylheptanethioate 22d

Compound **22d** [73% yield of a mixture of 94% *syn*-**22d** and 6% of *anti*-**22d**, $[\alpha]_D^{20} = -4.8$ (*c* 1.0, $CHCl_3$), colorless oil]. ^{1}H NMR δ 7.42–7.34 (m, 2H), 7.33–7.24 (m, 3H), 2.98 (q, *J* = 7.4 Hz, 2H), 2.83–2.73 (m, 1H), 2.72–2.58 (m, 2H), 2.40 (dd, *J* = 14.4 Hz, 8.3 Hz, 1H), 2.30–2.17 (m, 1H), 1.81–1.59 (m, 2H), 1.58–1.47 (m, 1H), 1.47–1.39 (m, 1H), 1.35 (t, *J* = 7.4 Hz, 3H), 1.15 (ddd, *J* = 11.6 Hz, 10.2 Hz, 7.0 Hz, 1H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H); residual peaks *anti*-product: 2.56 (1H), 2.47 (dd, *J* = 14.4, 7.8 Hz, 1H); ^{13}C NMR δ 199.37 (C), 143.00 (C), 128.40 (2 × CH), 125.70 (CH), 51.38 (CH_2), 44.44 (CH_2), 38.55 (CH_2), 33.28 (CH_2), 29.83 (CH), 28.75 (CH), 23.41 (CH_2), 20.23 (CH_3), 20.11 (CH_3), 14.96 (CH_3); residual peaks *anti*-product: 44.12 (CH_2), 19.38 (CH_3); MS *m*/*z* 217 (M^+−SEt, 13), 91 ($C_6H_5CH_2$, 100); HRMS calcd for $C_{17}H_{27}OS$ 279.1783, found 279.1777.

Ratio of *syn*- and *anti*-product was determined by ^{13}C NMR with 10 s d1-time.

4.5.5. (3*S*,5*S*)-*S*-Ethyl 8-(benzyloxy)-3,5-dimethyloctanethioate 22e

This product was purified with flash chromatography (gradient 1:99 to 5:95 Et_2O/pentane). [64% yield of a mixture of 94% *syn*-**22e** and 6% of *anti*-**22e**, $[\alpha]_D^{20} = -2.8$ (*c* 1.0, CH_2Cl_2), colorless oil]. ^{1}H NMR δ 7.38–7.24 (m, 5H), 4.51 (d, *J* = 2.1 Hz, 2H), 3.45 (td, *J* = 6.7 Hz, 2.3 Hz, 2H), 2.87 (qd, *J* = 7.4 Hz, 2.5 Hz, 2H), 2.52 (ddd, *J* = 14.4 Hz, 5.3 Hz, 2.3 Hz, 1H), 2.28 (ddd, *J* = 14.4 Hz, 8.5 Hz, 2.5 Hz, 1H), 2.18–2.06 (m, 1H), 1.73–1.63 (m, 1H), 1.63–1.53 (m, 1H), 1.53–1.44 (m, 1H), 1.44–1.34 (m, 1H), 1.31–1.19 (m, 4H), 1.19–1.08 (m, 1H), 1.08–0.98 (m, 1H), 0.93 (dd, *J* = 6.6 Hz, 2.4 Hz, 3H), 0.89 (dd, *J* = 6.5 Hz, 2.4 Hz, 3H); ^{13}C NMR δ 199.37 (C), 138.77 (C), 128.44 (CH), 127.75 (CH), 127.58 (CH), 73.00 (CH_2), 70.87 (CH_2), 51.33 (CH_2), 44.58 (CH_2), 33.08 (CH_2), 30.02 (CH), 28.74 (CH), 27.20 (CH_2), 23.39 (CH_2), 20.31 (CH_3), 20.06 (CH_3), 14.95 (CH_3); MS *m*/*z* 322 (M^+, 1), 91 ($C_6H_5CH_2$, 100); HRMS calcd for $C_{19}H_{30}O_2S$ 323.2039, found 323.2036.

Ratio of *syn*- and *anti*-product was determined by ^{13}C NMR with 10 s d1-time.

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‡‡‡‡ This reaction was performed from 0.3 mmol up to 5.0 mmol scale.

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